OCT 10 2002
PATENT & TRADEMARK OFFICE

Office Action Summary

Application No.	Applicant(s)	
09/631241	Marzolin et al	
Examiner	Group Art Unit	
Hall	1657	

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 10/23/01.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-79 + 81-88 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-79 + 81-88 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 10/23/01 has been entered.

The amendment of 10/23/01 has been entered. The amendment amended claims 1-10, 12, 14-19, 23, 27, 30-36, 39, 45-47, 52-56 and 84, and added new claims 86-88.

Claims examined on the merits are 1-79 and 81-88 which are all claims in the application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendment filed 10/23/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the text added to page 69 by the amendment. It is not clear from Figure 8 that at 30° C, the crosslinked crystals are about 30% to about 80% as soluble as an uncrosslinked counterpart protein crystal when stored in phosphate buffered saline solution for between about 100 and about 350 hours. Figure 8 does not show any temperature and comparing percent solubility with stored uncrosslinked crystals as recited. While Figure 8 shows percent protein in solution, there is no percent range as now recited by page 69.

Furthermore, while Figure 8 is based on Example 13, there is found inadequate basis in Example 13 for the interpretation of Figure 8 as now set forth by page 69.

Applicant is required to cancel the new matter in the reply to this Office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-79 and 81-88 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Adequate support is not found in the specification for insertion a) in claims 1, 17, 18 and 54 and insertion b) in claims 55 and 56 that recites "between about 30% and about 80% as soluble as an uncrosslinked counterpart of said protein crystal when stored in phosphate buffered saline solution at about 30° C for between about 100 hours and about 350 hours".

Adequate support is not found in the specification for reciting "releasing between about 0.1% and about 100% of crystalline protein as soluble protein per day" in b) of claims 1, 17, 18 and 54, c) of claim 55 and a) of claim 56.

Adequate support is not found in the specification for reciting in claim 19 "the amino acid residues involved in the crosslinks, whether the crosslinker is homobifunctional or heterobifunctional".

Adequate support is not found in the specification for reciting in claim 86 "releasing about 100% of crystalline protein as soluble protein per day", in claim 87 "releasing about 100% of crystalline protein as soluble protein per hour" and in claim 88 "releasing between about 1% and about 50% of crystalline protein as soluble protein per minute".

There is inadequate support in the specification for soluble protein being formed as now claimed by any of the environment changes claimed as resulting in soluble protein formation.

Applicants have cited various portions of specification and Figure 8 as providing support. However, these portions of the specification and Figure 8 do not contain the recitations of the claims as noted above, and it is not clear how the specification supports the recited claim limitations.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-79 and 81-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are confusing and unclear as to specific environment changes that will result in soluble protein being formed as claimed. The specification fails to support that any environment change within the scope of environment changes claimed will provide the claimed solubility.

Claims 54-56 are confusing and unclear by requiring reacting with a first and second crosslinking agent as an alternative to reacting with only a first crosslinking agent since it is uncertain as to the difference in process steps used when two crosslinking agents are use as compared to when using only one crosslinking agent. Furthermore, it is unclear as to whether the first crosslinking agent when used alone is the same as when used with a second crosslinking agent. When only one crosslinking agent is used, it is confusing to require a first crosslinking agent since there is no second crosslinking agent. It is suggested that using a first and second crosslinking agent be deleted from claims 54-56, and this alternative be claimed in separate independent claims. Also, not require a first crosslinking agent when only one crosslinking agent is used.

The difference in claims 54 and 56 is unclear. Unless a difference can be pointed out, one of the claims should be deleted.

In line 6 of claims 67, 70, 71 and 73, and line 5 of claims 68 and 72, "a" before "crosslinking" should be changed to "the" to be clear as to the crosslinking agent required.

Claims 67-73 are confusing by being unclear as to whether the crosslinking agent and amount required relates to the use of only a first crosslinking agent or to using a first and second crosslinking agent. If

the latter, it is unclear as to whether the crosslinking agent is the first or second.

Claims 67-73 are unclear as to whether the claims are requiring the alternative of using only a first crosslinking agent, or are specifying crosslinking conditions that are used should this alternative be selected.

Claims 74 and 75 are unclear as to whether the claims are requiring the alternative of using a first and second crosslinking agent, or are specifying crosslinking conditions that are used should this alternative be selected.

Claims 1-44, 46-63, 76 and 81-88 are rejected under 35 U.S.C. 102(a) as anticipated by Navia et al (5,618,710).

The claims are drawn to crosslinked protein crystals and methods for preparation thereof wherein the crosslinked protein crystals can be changed from insoluble form to soluble form by a change in temperature, pH, chemical composition, dilution form or shear force acting on the crystal. In claim 1, the crosslinked protein crystal is required to be between about 30% and about 80% as soluble as an uncrosslinked counterpart of said protein crystal when stored in phosphate buffered saline solution at about 30° C for between about 100 hours and about 350 hours and to release between about 0.1% and about 100% of crystalline protein as soluble protein per day. Claims 86 and 87 require releasing about 100% soluble protein per day and per hour, respectively, and claim 88 requires releasing about 1% to about 50% soluble protein per minute.

Navia et al disclose crosslinked protein crystals that will inherently be capable of being changed to soluble form as claimed by one

or more of the claimed environment changes since the crosslinked protein crystals disclosed by Navia et al can be prepared using crosslinking conditions that will result in essentially the same or less crosslinking than obtained when using crosslinking conditions disclosed in the present specification. For example, in Navia et al in example 2 (col 37, lines 32-35), 12.5% glutaraldehyde is used for 3 hours, in example 4 (col 43, lines 48-52), 5.77% glutaraldehyde is used for one hour, in example 5 (col 44, lines 56-61) and 6 (col 45, lines 64-67), 12.5% glutaraldehyde is used for one hour, in example 7 (col 46, lines 50-55), 24% glutaraldehyde is used for 20 minutes, in example 9 (col 48, line 40), 2% glutaraldehyde is used, and in example 10 (col 51, lines 15-18), 7.5% glutaraldehyde is used for 30 minutes. In the present specification, in example 18, the final glutaraldehyde concentration is 4% and crosslinking is for 24 hours. These conditions appear to also be used in examples 19 and 20. In example 22, 6.5% glutaraldehyde is used for one hour and in example 23, 6.0% glutaraldehyde is used for one hour. Thus, it is apparent that the crosslinking conditions used by Navia et al are essentially equivalent to those disclosed by the present specification and would not have resulted in a substantially greater amount of crosslinking. While Navia et al may use a higher amount of crosslinking agent in certain instances, the time for crosslinking is less than disclosed in the present specification when using a lower amount of crosslinking agent. Using 7.5% glutaraldehyde for 30 minutes or 5.77% glutaraldehyde for one hour as in Navia et al is not going to result in more crosslinking than when using 6.5% or 6.0% glutaraldehyde for one hour or using 4% glutaraldehyde for 24 hours as in the present

specification. Similarly, using 24% glutaraldehyde for 20 minutes or 12.5% glutaraldehyde for one hour will not result in substantially more crosslinking than using 4% glutaraldehyde for 24 hours.

Applicant's arguments filed 10/23/01 have been fully considered but they are not persuasive.

Applicants urge that the objective of Navia et al is to produce insoluble crosslinked protein crystals that do not dissolve, and the crosslinked protein crystals of Navia et al do not have the solubility characteristics of the claimed crosslinked protein crystals. However, the claimed crosslinked protein crystals are insoluble until subjected to an environment change that will dissolve the crosslinked crystals. Since Navia et al may use essentially equivalent crosslinking conditions as disclosed in the present specification, it appears the crosslinked protein crystals of Navia et al prepared using these equivalent crosslinking conditions will dissolve as claimed when subjected to the same change in environment that causes dissolving. The fact that the crosslinked protein crystals of Navia et al do not dissolve under the conditions which Navia et al use the crystals does not preclude the crystals from dissolving under conditions that have not been used by Navia et al.

Applicants argue that the crosslinked protein crystals of the present claims are produced to have an intermediate level of crosslinking that results in the claimed solubility characteristics. However, when comparing the examples of Navia et al with those of the present specification as set forth above, it becomes apparent that the level of

crosslinking obtained by Navia et al can be essentially the same as obtained when using crosslinking conditions in the present specification.

Applicants urge that examples of Navia et al show crosslinked enzyme crystals having no loss in enzyme activity after days or months, and this supports that the crosslinked crystals of Navia et al exhibit a solubility stability outside the claimed range. However, retaining enzyme activity does not mean that dissolving does not occur since the enzyme can have activity after the crosslinked enzyme crystals dissolve. Furthermore, there is inadequate evidence to establish that the claimed crosslinked protein crystals when prepared using crosslinking conditions in the present specification closest to those disclosed by Navia et al will not have stable activity under test storage conditions used by Navia et al.

Claims 45 and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navia et al.

It would have been obvious to use a crosslinked enzyme crystal such as a protease produced as disclosed by Navia et al in a detergent formulation as required by claim 45 since it is conventional to use enzymes such as proteases in detergent formulations and Navia et al disclose using crosslinked enzyme crystals for uses where enzymes are conventionally used.

It would have been a matter of obvious choice to use known crosslinking agents other than disclosed by Navia et al as in claims 64-66 since the other crosslinking agents would been expected to provide crosslinked protein crystals.

The comments set forth above in response to arguments also apply to this rejection.

Claims 1-79 and 81-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Navia et al in view of Neville et al (5,066,490) and Kausch et al (5,508,164).

In additional to the invention as described above, claims 77-79 require a reversible crosslinking agent which can be a disulfide crosslinking agent.

Neville et al disclose using a reversible crosslinking agents for linking an amino group containing substance to a group on a second compound so the crosslinking agent can be cleaved to release the substance.

Kausch et al disclose using disulfide crosslinking agents for reversible immobilization (col 6, lines 52-68).

It would have been obvious to use a reversible crosslinking agent such as a disulfide crosslinking agent as the crosslinking agent of Navia et al to obtain reversible immobilization as suggested by Neville et al and Kausch et al. As to claims 67-75, these claims merely set forth conditions used should be one alternative of using one or two crosslinking agents be selected. Since the alternative is not required to be selected, the conditions of the claims do not have to be used.

The comments set forth above in response to arguments also apply to this rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-76 and 81-88 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,140,475. Although the conflicting claims are not identical, they are not patentably distinct from each other because crosslinked protein crystals that dissolve as presently claimed and method for preparation thereof as presently claimed would have been obvious from the method of the claims of the patent that produces crosslinked protein crystals that dissolve as a result of a change in environment that can be the same as required by the present claims.

Claims 77-79 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,140,475 in view of Neville et al (5,066,490) and Kausch et al (5,508,164). For the type of reasons set forth above when applying Neville et al and Kausch et al, it would have been obvious to use a reversible crosslinking agent such as a disulfide crosslinking agent as the crosslinking agent of the patent claims to obtain reversible immobilization as suggested by Neville et al and Kausch et al.

Claims 67-73 would be free of the prior art if the alternative of using a first crosslinking agent is required to be carried out and the crosslinking conditions of these claims are required. Claims 74 and 75 would be free of the prior art if the alternative of using a first and second crosslinking agent is required to be carrier out and the crosslinking conditions of these claims are required.

Should amendments directed to overcoming any of the above rejections render any claims the same as any of the claims of Patent No. 6,140,475, the claims will be rejected on 35 U.S.C. 101 double patenting.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is (703) 308-0520. The examiner can normally be reached on Monday-Thursday and every other Friday from about 8:30 AM to about 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, a message can be left on voice mail.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn, can be reached at telephone number (703) 308-4743.

The fax phone number is (703) 872-9306 before final rejection or (703) 872-9307 after final rejection.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DMN
3/29/02

DAVID M. NAFF
PRIMARY EXAMINER
ART UNIT 1657